HED DOC. NO. 013579

DATE: **July 21, 1999**

MEMORANDUM

SUBJECT: ***OXYDEMETON METHYL (ODM)*** **- REVISED HIARC REPORT-** Report of the Hazard Identification Assessment Review Committee.

FROM: Robert F. Fricke
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THROUGH: Jess Rowland, Co-Chair
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Health Effects Division (7509C)
and
Pauline Wagner, Co-Chair
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TO: Alan Nielsen, Branch Senior Scientist
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PC Code: 058702

On July 8, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed a toxicokinetic study (00152368) with ODM to evaluate the effect of this study on the acceptability of a previously reviewed alkaline elution assay in the rat (43776101) and its impact of the FQPA safety factor. **For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments and supersedes all other reports (RfD, TES, HIARC, etc) for ODM.**

Committee Members in Attendance

Members present were: David Andersen, Virginia Dobozy, Karen Hamernik, Pam Hurley, Mike Ioannou, Sue Makris, Nancy McCarroll, Jess Rowland, PV Shah, Brenda Tarplee (Executive Secretary)

Other HED staff present at the meeting was Paula Deschamp

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Brenda Tarplee
Executive Secretary
Hazard Identification Assessment Review Committee

I. BACKGROUND

Oxydemeton methyl (ODM) was reviewed by the Health Effects Division-Hazard Identification Assessment Committee (HIARC) meetings of July 1 and 2, 1997 (memorandum dated July 24, 1997) and February 16, 1999 (memorandum dated June 21, 1999) and by the Health Effects Division Toxicology Endpoint Selection (TES) Committee (document dated May 1, 1997).

On February 25, 1998, the HIARC met again to re-evaluate the toxicological endpoints for acute and chronic dietary as well as occupational and residential (dermal and inhalation) exposure risk assessments in light of a recently submitted 7-day dermal toxicity study. The HIARC determined that the application of the FQPA safety factor for the protection of infants and children from exposure to ODM, as required by FQPA, will be determined by the FQPA Safety Factor Committee (HIARC Report dated May 7, 1998; HED Doc No. 012606).

On July 27, 1998, the Agency announced that it is deeply concerned about the conduct of pesticide health effects on human subjects and consulted with the FIFRA Scientific Advisory Panel and the Scientific Advisory Board (SAP/SAB) about the application of stringent ethical standards to any studies. The SAP/SAB discussed the use of the human studies at their meetings on December 10 and 11, 1998. At this time, the Agency has not yet received the response to its consultation with the SAP/SAB and is continuing to work on its approach to the critical ethical questions.

In light of the developing Agency policy on use of toxicology studies employing human subjects, and pending reassessment of human studies for considerations of the ethical acceptability of such studies, HED has reconsidered the toxicology database for ODM and has for the chronic dietary risk assessment, used a toxicology endpoint from an animals study.

On February 16, 1999, HIARC evaluated the doses and toxicology endpoints selected for ODM based solely on animal toxicity studies. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk.

II. REVIEW OF ADDITIONAL DATA

On July 8, 1999, the HIARC evaluated the merit of a toxicokinetic study in the rat (00152368), and the impact of this study on the acceptability of a previously submitted and reviewed *in vivo* alkaline elution assay in the rat (43776101). The alkaline elution assay was previously graded as unacceptable because there was concern that exposure to oxydemeton methyl may not have had enough time (4 hours) to allow for sufficient interaction with the target organ (testes).

The Registrant has submitted a toxicokinetic study with oxydemeton methyl in the rat in which the blood and tissue distribution (including the testes) was measured over a time course of 20 minutes to 10 days post-dosing. The toxicokinetic study clearly demonstrated that after 4 hours, oxydemeton methyl had enough time to distribute throughout the body, and that the testes were adequately exposed during this time. Because there was no longer any concern about the adequacy of the time used in the alkaline elution assay, he HIARC agreed that the *in vivo* alkaline elution assay in the rat was acceptable.

The acceptability of the alkaline elution assay, in conjunction with the negative results of this assay as well as the negative findings of the dominant lethal assays, lowered the concern for heritable effects from exposure to ODM and obliged the HIARC to evaluate the results of the mouse spot test critically. The primary function of the mouse spot test is as a carcinogenesis screening tool. Although ODM was positive in this test system, it was negative in other in vivo assays with somatic cells. In addition, ODM was shown to be non-carcinogenic in CD-1 mice and Fischer 344 rats.

Based on a weight-of-evidence re-evaluation, the HIARC concluded that the genetic concern resulting from exposure to ODM have been addressed. The requirement for the mouse specific locus test, which evaluates adverse effect on germinal cells, is revoked. Therefore, the toxicology database for ODM is now complete.

For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments.

III. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD)

Study Selected: Acute Neurotoxicity Study in the Rat §81-8

MRID No. 43929901

Executive Summary: In an acute neurotoxicity study, four groups of 42/sex Sprague-Dawley Crl:CD^{R}(SD)BR strain rats were dosed at 0 (control), 2.5, 10 or 50 mg/kg of ODM (dose in terms of a.i., the study report indicates the doses were 5, 20 and 100 mg/kg of a 50% formulation in methylisobutylketone stabilizer) in water by gavage. Animals (12/sex/dose) were assessed for FOB (peak time of effect of 1.5 to 1.75 hours post dosing) and motor activity (1.75-2.25 hours post dosing) and 10/sex/dose were assessed for plasma, RBC and brain cholinesterase (ChE) at the peak time of effect and again on days 7 and 15. At 10 mg/kg there were tremors, ataxic gait and pinpoint pupils, decreases in rearing, arousal response, defecation, visual placement, pinch responses, body temperature and motor activity. At 50 mg/kg there were deaths and some 15 other FOB parameters affected to indicate both motor and sensory impairment and body weight decrease. Plasma (45%♂, 58%♀), RBC (38%♂, 30%♀) and brain ChE (45%♂, 39%♀) were all inhibited at 2.5 mg/kg when assessed at approximately 1.5 hours postdosing. The 10 and 50 mg/kg dose groups showed progressively more inhibition. Brain ChE recovered slowly but remained inhibited at day 15.

Dose/Endpoint for establishing the Acute RfD: LOAEL = 2.5 mg/kg/day, based on inhibition of plasma, RBC, and brain ChE. The NOAEL was not established.

Uncertainty Factor (UF): UF = 300 (10x for inter-species extrapolation, 10x for intra-species variability, and 3x for the use of a LOAEL).

Acute RfD = 2.5 mg/kg/day (LOAEL) / 300 (UF) = **0.008 mg/kg/day**

Comments about study, endpoint and UF: **No change from the previous dose/endpoint selected based on the rat study (i.e., human data was not used previously).** This dose/end point is appropriate for this risk assessment since it was observed following a single dose (exposure). The HIARC report dated May 7, 1998 applied a 10x FIFRA safety factor for datagap in lieu of a specific locus test. This factor was considered an FQPA safety factor during the comprehensive review of the OPs (May, 1998). This factor is NOT applied to derive the current acute RfD since the concern for the heritable effects have been addressed and the requirement for a mouse specific locus test is revoked.

This risk assessment is required.

B. Chronic Dietary RfD

Study Selected: Chronic Toxicity-Dog §83-1b

MRID No.: 00151805, 41980801 and 43454201)

Executive Summary: Groups of beagle dogs (6/sex/dose) received oxydemeton methyl via intubation at doses of 0.0125, 0.125, or 1.25 mg/kg/day for 52 weeks. Doses were adjusted for individual animal body weights on a weekly basis. The dosing volume was 10 ml/kg; control dogs received 10 ml/kg tap water. Dogs were intubated daily, 1-3 hours before morning feeding. The NOAEL was 0.0125 mg/kg/day and the LOAEL was 0.125 mg/kg/day based on inhibition of plasma, erythrocyte and brain cholinesterase activity in both sexes of dogs.

Dose and Endpoint for Risk Assessment: NOAEL=0.0125 mg/kg based on plasma, erythrocyte and brain cholinesterase inhibition in males and females at 0.125 mg/kg (LOAEL).

Uncertainty Factor: 100 (10x for inter-species variation and 10x for intra-species extrapolation).

Chronic RfD = 0.0125 mg/kg/day (NOAEL) / 100 (UF) = **0.000125 mg/kg**

Comments about study, endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC concluded that the 10x inter-species extrapolation factor cannot be modified/altered. The study in humans (Doull *et al.* 1972) is useful only as *supplemental* data. Although this study provided

supportive scientific data, it is not appropriate for use in risk assessment and the treatment regimen (25-30-days in four subjects and 2 subjects for 60 days) is not adequate to characterize lifetime exposure. Additionally, cholinesterase inhibition did not reach steady state until 2-24 months in rats and there is uncertainty as to when this occurs in humans. There is concern for the occurrence of brain cholinesterase inhibition (not measurable in humans) at the same dose levels as plasma cholinesterase inhibition in animals. Data from the animal studies demonstrate that plasma, red blood cell, and brain cholinesterase inhibition occur at the same dose levels in both sexes of rats (90-day neurotoxicity study) and in dogs (chronic study). Therefore, no comparison of dose and effects in humans and animals could be made.

The HIARC report dated May 7, 1998 applied a 10x FIFRA safety factor for datagap in lieu of a specific locus test. This factor was considered an FQPA Safety Factor during the comprehensive review of the Ops (May, 1998). This factor is NOT applied to derive the current acute RfD since the concern for the heritable effects have been addressed and the requirement for a mouse specific locus test is revoked.

C. Occupational/Residential Exposure

There are no registered residential uses at the present time. Therefore, the following risk assessments are applicable only for occupational exposures.

1. Dermal Absorption

MRID No.: 001638631

Dermal Absorption Factor: Dermal absorption was calculated to be 50.4% for males and 51.8% for females. The dermal absorption rates as calculated by regression analysis based on mg equivalents of ^{14}C-ODM over time were 0.15 μg/cm^2/hour for males and 0.17 μg/cm^2/hour for females.

2. Short-Term Dermal (1-7 Days)

Study Selected: 7-Day Dermal Toxicity Study in the Rat

MRID No. None assigned (preliminary data submission by the registrant)

Executive Summary: ODM was administered dermally in water to Sprague- Dawley rats (10/sex/dose) at doses of 0, 1.5, 5.0, 10.0 or 20.0 mg/kg/day, 6 hours/day, for 7 days.

All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Further, no body weight decrements or effects on food consumption occurred. At terminal sacrifice, no treatment-related gross necropsy findings were reported.

At day 7, statistically significant inhibition of RBC and brain ChE activities were observed, plasma ChE activity was not inhibited by treatment. RBC ChE activity of males dosed at 10 and 20 mg/kg/day was inhibited by 12% and 25%, respectively, and brain ChE activity by 8.2 and 12%, respectively. Brain ChE activity in females was inhibited by 14% at 20

mg/kg/day. Plasma ChE activity in males and females and RBC ChE activity in females were comparable to control values.

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on significant inhibition of RBC and brain ChE in males (12% and 8.2%, respectively) at 10 mg/kg/day (LOAEL).

Comments about Study and Endpoint: **No change from the previous dose/endpoint selected based on the rat study (i.e., human data was not used previously).** For the 14-day dermal toxicity study, plasma and erythrocyte ChE activities were measured at 7 days and 14 days; while brain ChE activity was measured only at 14 days. In the 7-day dermal toxicity study, plasma, erythrocyte and brain ChE activities were all measured at 7 days. For this reason, the 7-day dermal toxicity study was selected over the 14-day dermal toxicity study. Further, there was no consistency in the results of the two studies (plasma and erythrocyte ChE inhibition at 5 mg/kg/day differed greatly between the two studies). The rationale provided by the Registrant was not adequate to reject the 14-day study as flawed.

This Risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 14-Day Dermal Toxicity Study in the Rat

MRID No. 40499304

Executive Summary: ODM (94.6%), was administered dermally in water to five Sprague Dawley rats per sex per group, 6 hour per day, for 14 days at 0, 0.3, 1.0, and 5.0 mg/kg/day . Plasma ChE and RBC ChE activity was determined at day 0, 7, and 14. Brain ChE activity was determined at termination. No effects were seen on body weight or food consumption. No treatment-related clinical findings or necropsy observations were observed. No biologically significant inhibition of plasma or erythrocyte ChE was observed in low-, mid- or high-dose males and females on day 0. At day 7, significant inhibition of plasma and erythrocyte ChE was observed in high-dose males (38% and 26%, respectively) and females (40% and 28%, respectively). At day 14, plasma ChE was inhibited only in high-dose females (55%), while erythrocyte ChE was inhibited in mid-dose females (11%) and high-dose males (37%) and females (46%). Brain ChE activity, measured at day 14, was inhibited in mid- and high-dose males (12% and 48%, respectively) and low-, mid- and high-dose females (11%, 16% and 60%, respectively). Dose and Endpoint for Risk Assessment: NOAEL = 0.3 mg/kg./day for brain ChE inhibition in males.

Comments about Study and Endpoint: **No change from the previous dose/endpoint selected based on the rat study (i.e., human data was not used previously).** This study was conduced via the appropriate route of concern (i.e., dermal) for this risk assessment.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID No. None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: Based on the current use pattern, there is minimal concern for long term dermal exposure potential/risk.

This risk assessment is NOT required

5. Inhalation Exposure (Any Time Period)

Study Selected: Acute inhalation study in the rat (81-3)

MRID Nos. 40779805C and 40779805

Executive Summary: In an acute inhalation toxicity study, groups of young adult Sprague Dawley rats were exposed by the inhalation route to ODM (50% concentrate, 55.3% a.i. in 50% polyethylene glycol 400 and 50% ethanol) for 4 hours (nose only) at concentrations of 0.177, 0.224, 0.266, 0.370 or 0.540 mg/L. Animals then were observed for 14 days. The LC_{50} for males was 0.443 mg/L and for females was 0.427 mg/L. The NOAEL was <0.177 mg/L or < 0.0979 mg a.i./L based on clinical signs (tremors) in males and females (note: dose levels should be multiplied by 0.553 to adjust for percent active ingredient).

Dose dependent mortality was seen at ≥ 0.266 mg/L in males and females. Death occurred on the day of dosing to day 5 after dosing. Most deaths occurred on day 0 to 2, with only 1 male dying on day 5 and 1 female dying on day 3. Tremors were seen in most males and females at all dose levels. In addition, hypoactivity and salivation were seen in most males and females at ≥ 0.224 mg/L. Clinical signs ended by day 7. There appeared to be body weight gain decreases in females at ≥ 0.370 mg/L and in males at ≥ 0.224 mg/L. Single necropsy findings occurred more frequently at ≥ 0.266 in males and ≥ 0.0.370 mg/L in females, such as salivation, turbinates red, ventrum staining and black zone in the glandular stomach mucosa. No compound related lesions were seen in animals that survived to day 14.

Dose and Endpoint for Risk Assessment: Dose=0.098 mg/L; the LOAEL of 0.177 mg/L adjusted for percent active ingredient (0.177 x 0.553). A NOAEL was not established.

Comments about Study and Endpoints: Since no other inhalation studies were available, the HIARC recommended that this dose be used for short, intermediate and chronic exposure risk assessments. Since a LOAEL was used a MOE of 300 is required for this

exposure scenario.

This risk assessment is required.

D. Margin of Exposure for Occupational/Residential Exposures

There are nor residential uses at the present time. For occupational exposure risk assessments, a MOE of 100 is required for dermal exposures and a MOE of 300 (due to the use of a LOAEL) is required for inhalation exposures.

E. Recommendation for Aggregate Exposure (food, water and residential) Risk Assessments

Since there are no residential uses, aggregate exposure risk assessments will be limited to food and water.

For **acute** aggregate dietary exposure risk assessment, combine the high end exposure values from food plus water.

For **chronic** aggregate dietary exposure risk assessment combine the average values from food plus water.

IV. FQPA ASSESSMENT

The FQPA Safety Factor Committee, during its evaluation of the hazard and exposure data on June 15 and 16, 1998, recommended that the 10x FQPA safety factor should be retained for ODM because of the concern for heritable effects as demonstrated in an in vivo mouse spot test. In addition, there was valid evidence of DNA strand breaks in rat testes cells in an in vitro alkaline elution assay (FQPA Safety Factor Recommendations for the Organophosphates, dated August 6, 1998).

Since then the Registrant has submitted appropriate data to alleviate the concerns associated with the alkaline elution assay and this study is now classified as acceptable. In addition, the HIARC has concluded that the genetic concerns results from exposure to ODM have been addressed and consequently has revoked the requirement for a mouse spot test. Based on hazard alone, the HIARC recommended that the 10x factor is not required for ODM. The final recommendation will be made by the FQPA Safety Factor Committee.

V. ACUTE TOXICITY

Study Type	Animal	MRID No	Results	Toxicity Category
81-1: Acute Oral	Rat	40779801	Female: LD_{50} = 48 mg/kg	I
81-2: Acute Dermal	Rat	00143350	Female: LD_{50} = 112 mg/kg	I
81-4: Primary Eye Irritation	Rabbit	00151801	Slightly irritating	III
81-5: Primary Dermal Irritation	Rabbit	00151801	Non-irritating	IV
81-6: Dermal Sensitization	Guinea Pig	40779802	Not a skin sensitizer (Beuhler)	N/A

V. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints and margins of exposure for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE[a]
Acute Dietary	LOAEL=2.5	Decreased Plasma, RBC and brain ChE activity in males	Acute Neurotoxicity in the rat	NA
	UF=300	**Acute RfD = 0.008 mg/kg/day**		
Chronic Dietary (Non-cancer)	NOAEL=0.0125	Erythrocyte and brain ChE activity	Chronic-Dog	NA
	UF=100	**Chronic RfD = 0.000125 mg/kg/day**		
Carcinogenicity (Dietary)	Classified as a **"Not Likely"** human carcinogen.			
Dermal Absorption	Calculated to be 50.4% for males and 51.8% for females			
Short-Term (Dermal)	Dermal NOAEL=5.0	Decreases in RBC and brain ChE activity	7-Day Dermal Toxicity-Rat	100
Intermediate-Term (Dermal)	Dermal NOAEL=0.3	Decreased brain ChE activity	14-Day Dermal Toxicity -Rat	100
Inhalation (any time period)	Inhalation LOAEL = 0.098 mg/L	Clinical signs (tremors)	Acute Inhalation - Rat	300 [b]

a = MOEs are of occupational exposure only; no residential uses at this time.

b = MOE 300 required due to use of a LOAEL.